CHALLENGES TO INFORMED CONSENT FOR EXOME SEQUENCING: A BEST WORST SCALING EXPERIMENT

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A Thesis Submitted to the Johns Hopkins University in Conformity with the requirements for the degree of Master of Science

Baltimore, Maryland
January 2018

ABSTRACT

Background: As exome sequencing expands as a diagnostic tool, patients and providers have voiced concerns about the breadth and scope of potential results. Particularly, genetic counselors perceive challenges to prioritizing complex information during informed consent sessions.

Objectives: This study first sought to characterize challenges to the informed consent process for exome sequencing. Secondly, it aimed to understand how genetic counselors prioritize elements of obtaining consent for clinical exome sequencing, and thirdly, whether counselor factors influence prioritization.

Methods: Aim one was addressed through a systematic review of the published literature from January 2010 to February 2017. Seventeen identified challenges culled from the review informed the development of a best worst scale (BWS) used to address aim two. Eleven attributes for the BWS task were finalized with input from two focus groups and were assembled into choice sets using a balanced incomplete block design. A survey presenting the BWS tasks and assessing perceptions of communication and target efficacy and tolerance for ambiguity alongside demographics was assembled to address aim three. The survey was distributed to members of the National Society of Genetic Counselors via their email listserv. BWS data was analyzed using a counts based method, and stratified analyses were run with two-tailed t tests controlling for reported counselor factors.

Results: 342 genetic counselors completed the survey. Counselors with more experience ordering exome sequencing were significantly more likely to work in pediatrics and reported higher communication and target efficacy. Ranking of best-worst scores

revealed that genetic counselors prioritize collaborative decision-making, assessing patient understanding and managing expectations, with the least emphasis placed on discussing technological complexities. Stratified analyses found that counselors with more exome experience, and those who reported higher target efficacy, were significantly more likely to prioritize discussion of variants of uncertain significance ($p<0.05$).

Discussion: Genetic counselors perceive challenges in addressing the many complicated aspects of exome sequencing, particularly secondary findings and limitations of testing. Counselors report intentions to prioritize aspects of informed consent that focus on addressing individual patient needs. Additionally, participant characteristics influence discussion of potential uncertain results. Further research should explore how these priorities are exhibited in practice.

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ACKNOWLEDGEMENTS

To my advisor, Barbara Biesecker: You have been a mentor to me throughout my time in the program. Thank you for always pushing me to think critically, and for supporting me through times when this was challenging. Your enthusiasm and belief in this project has kept me moving forward when I felt discouraged. I am so excited to see what your new research projects will bring, and look forward to working together into the future!

To my committee members, Julie Cohen and John Bridges: You each brought a unique perspective that was essential to shaping the study. Thank you Julie, for imparting your clinical experience and John, for sharing your expertise in best worst scaling methodology. Also, with thanks to Holly Peay for your advice in designing and carrying out the best worst scaling analyses.

To Lori Erby: Thank you for your compassionate guidance from the very beginning. You approached the challenges of proposal development with patience, creativity and kindness. I have learned so much from you.

To my study participants: Thank you for sharing your insights and experiences, I am eager to see how the field of genetic counseling will continue to grow and adapt to the development of new technologies. I would especially like to thank those who participated in the focus groups; your input was instrumental to furthering the study.

To my classmates, Anna, Annie, Emily and Hannah: I could not imagine the past two and a half years without all of you. We all bring something different and have built a strong and close group. I am so thankful for your friendship, and both the fun and more difficult times that we have made it through together. You have all inspired me to never stop questioning and to never accept things as they are. It will be incredibly hard to adjust to not seeing you every week, but I know that we will always have our shared brain!

To my family and friends, especially Mom, Dad, David and Matt: Your confidence in my ability to reach this goal has meant so much. Thank you for always making me laugh and being available to talk through things, often multiple times. I love you and feel so lucky to have you in my life.

This research study was funded by the National Human Genome Research Institute Intramural Research Program, National Institutes of Health.

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PART ONE: INTRODUCTION

Objectives and Specific Aims

Genomic sequencing is becoming increasingly incorporated into clinical and research practice as a molecular diagnostic tool. While there is much excitement surrounding the potential for this new technology, concerns about the breadth and uncertainty inherent to the testing methodology have been voiced by clinicians, researchers and patients (Bertier *et al.,* 2016; Levenseller *et al.,* 2014). The wide scope of possible results and evolving methods for data interpretation of information pose particular challenges to the informed consent process that must include discussion of the potential for secondary findings, variants of uncertain significance, and uninformative negative results (Bernhardt *et al,* 2015). Multiple stakeholders have reached a general consensus about the necessary content required for informed consent to exome sequencing, but variability persists in understanding how this information is prioritized and communicated (Ayuso *et al.,* 2013; ACMG Board of Directors, 2013). Genetic Counselors are often responsible for obtaining consent in both clinical and research settings, and have valuable insight to offer into how they approach consent for exome sequencing (Machini *et al.,* 2014).

Objective: This study seeks to understand challenges to the informed consent process for exome sequencing as perceived by healthcare providers, researchers and patients, as well as to explore how genetic counselors prioritize information and counseling elements when obtaining consent.

Aim 1: To characterize reported challenges to obtaining informed consent for exome sequencing through a systematic review of the published literature.

Aim 2: To understand how genetic counselors prioritize essential elements of informed consent for exome sequencing when approaching consent sessions in a pediatric clinical setting.

Aim 3: To explore whether prioritization of elements of informed consent is mediated by genetic counselor factors such as experience with exome sequencing, tolerance for ambiguity and perceived communication and target efficacies.

The results of this study will be presented in the form of two manuscripts. The first, entitled *Challenges to informed consent for genomic sequencing: a systematic literature review*, addresses Aim one. The second manuscript, *Challenges to informed consent for exome sequencing: a best worst scaling experiment,* describes the findings of a survey study designed to address Aims two and three.

Background and Literature Review

The Shift Towards Exome Sequencing & Challenges to Informed Consent

Exome sequencing has emerged as a novel tool for identifying disease causing and risk modifying variants throughout the genome, and has increasingly been offered as a step in the pediatric diagnostic process. Reports of the clinical utility of exome sequencing have demonstrated a 25-31% success rate in identifying pathogenic variants in patients referred for testing through a clinical laboratory due to a suspected genetic condition (Yang *et al.,* 2014; Farwell *et al.*, 2014). However, many questions have been

raised as to how this new technology will effectively become integrated into clinical practice, including the scope of information it can provide, how results will be interpreted and communicated to patients, and whether the infrastructure exists to support the transition (Biesecker *et al.,* 2012; Bertier *et al.,* 2016). This large-scale testing strategy represents a paradigm shift from traditional genetic testing that has targeted specific genes based on phenotypic data and familial risk assessment, as mutations may now be identified independently of the clinical indication (Hooker *et al.,* 2014). The possibility for secondary or incidental findings and the greater yield of variants of uncertain significance makes anticipation of an individual's results increasingly difficult.

These changes present considerable challenges to the informed consent process, which has previously involved discussion of the specific conditions under consideration. As results from exome sequencing cannot be predicted in advance, genetic counselors have discussed the need to expand and adapt the informed consent process to incorporate discussion of the inherent uncertainty and the potential for findings that cannot be interpreted clearly with current data (Bernhardt *et al.,* 2015). In order to organize the wide breadth of information, researchers and clinicians have aimed to identify a minimal list of information that must be included in the informed consent process for exome sequencing. Recommendations put forth by the ACMG Board of Directors broadly advocate for discussion of expected outcomes of testing including the type and likelihood of results that will or will not be returned, as well as the risks, benefits, limitations, alternatives to testing and potential implications for relatives (ACMG Board of Directors, 2013). A systematic review of fourteen papers published by professional societies or experts in the field identified seven domains necessary to obtaining informed consent that

were consistently referenced in the included studies. Broadly, these elements of the informed consent process were defined as: pre-test counseling, scope, description, benefits, risks, storage and future uses of test results, and management of incidental findings (Ayuso *et al.,* 2013).

While there appears to be consensus among researchers and clinicians about the necessary inclusion of these general elements, there is considerable heterogeneity in the specific content and level of detail provided under each domain. Content analysis of consent documents utilized in nine genomic research studies revealed evidence for significant variability in the descriptions of risks and benefits and in the categorization of potential result types (Henderson *et al.,* 2014). Furthermore, genetic counselors and research coordinators report varying their approach based on the setting, indication for testing, and age and health status of the patient (Bernhardt *et al.,* 2015).

In addition to the wide-ranging decisions about content and detail, the way that information is presented and prioritized is also highly variable in terms of length of time and style of communication (Arora *et al.,* 2016). Since it is impossible to predict the type of result that an individual can expect to receive, it becomes difficult to prioritize the elements of the informed consent process that will ultimately be most relevant to any given patient. Thus counselors must make decisions about which information to prioritize and how to present the content when time with patients is limited. A variety of techniques have been suggested including "binning" information about potential results into broader categories based on clinical relevance and presenting the information in a tiered fashion, though more research is needed to evaluate the outcomes of using these methods (Bradbury *et al,* 2015). A greater understanding of the factors influencing decisions about

which information to prioritize and how to communicate the scope of exome sequencing is needed to further develop these techniques and guide the evolution of the informed consent process (Khan *et al,* 2015).

The Communication Process and Informed Consent

In addition to characterizing the content of informed consent, previous research has also explored the communication process within genetic counseling sessions. Studies of the process of genetic counseling can help to continually refine goals and practice definitions, an area that may continue to develop as genetic counselors adapt to a changing field (Biesecker & Peters, 2001). Genetic counseling has been defined as "the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease" and incorporates interpretation, education and counseling (Resta *et al.,* 2006). Along these lines, studies of the communication process within genetic counseling sessions have suggested that information sharing strategies that are lower in counselor verbal dominance and higher in active exchange facilitate improved client understanding and satisfaction (Roter *et al.,* 2006).

Despite characterization of genetic counseling as a psychoeducational process, communication studies have identified educational information as the primary focus in the majority of genetic counseling sessions. In a recent systematic review of 22 published studies, the authors reported that counselor speech, often focused on biomedical and education content, dominated the session in several studies (Paul *et al.*, 2015). This pattern has also been observed in disclosure sessions for exome sequencing. Despite clear attempts to assess patient understanding, providers most often followed patients' reported

confusion with more complex biomedical information with minimal opportunities for interactivity (Walser *et al.,* 2017).

These findings suggest an apparent disconnect between genetic counselors' stated psychotherapeutic goals, and communication patterns that arise within the counseling session that focus primarily on addressing educational goals. The greater informational demand associated with informed consent for exome sequencing has the potential to exacerbate this discrepancy. Pediatric consent sessions are particularly challenging, as the decision to receive secondary findings could have potential consequences for the child's developing identity as well as other family members (Werner-Lin *et al.,* 2016). The importance of obtaining meaningful assent from children can also pose a challenge and complicate family decision-making. A study of 44 pediatric consent sessions in a clinical setting found that the majority of healthcare providers attempted to engage pediatric patients and that this was associated with a significant increase in child verbal participation (Miller *et al.,* 2017). Though parents are ultimately empowered to make testing decisions, child involvement is ethically important and may increase patients' ability to make informed decisions about future analysis of their sample after turning eighteen (Werner-Lin *et al.,* 2016).

As next generation sequencing enters clinical care, genetic counselors have an opportunity to play a critical role in addressing patient psychosocial and informational needs, though this transition will require increased attention to communication and counseling strategies used to convey the wide scope of possible testing outcomes (Austin *et al.,* 2014). Despite experience with more traditional models of informed consent, genetic counselors have voiced some trepidation about their abilities to effectively

communicate increasingly complex and uncertain information when obtaining informed consent for exome sequencing (Machini *et al.,* 2014). Multiple counselors involved in the informed consent process have reported feeling overwhelmed by the scope of exome sequencing when it was first introduced, but expressed a shift in their counseling style from information dominated to more patient-centered as they gained experience and comfort with the content (Bernhardt *et al.,* 2015*;* Wynn, 2016*).* A methodological shift from following the order of the consent form to summarizing main points and allowing patient questions to guide in-depth discussion has been described repeatedly. These observations suggest that doubts about one's ability to communicate effectively may influence information management decisions about the amount of information, content prioritization, and the degree of direct information sharing (Afifi & Weiner, 2004). A more thorough understanding of factors that contribute to the prioritization of different aspects of informed consent may help to identify barriers to patient-centered communication throughout the informed consent process.

Parent Informational Needs Surrounding Diagnostic Genomic Testing

Perceptions of parents' ability to understand and manage complex information central to the informed consent process may also play a contributory role in developing an approach to information sharing. Effective communication could be compromised if inaccurate assumptions are made about parents' abilities to process complicated information related to their child's diagnosis, both cognitively and emotionally. In contrast to some of the misgivings voiced by genetic counselors and the scientific community, patients and parents have been largely enthusiastic about the wealth of

information available through exome sequencing, and have expressed perceptions of their ability to adjust to multiple types of results (Sapp *et al.,* 2014; Krabbenborg *et al.,* 2016).

Similar concerns about patients' ability to cope with large-scale genomic data were raised in conjunction with the introduction of microarray technology. Multiple studies have addressed parental informational needs surrounding microarray testing as a pediatric diagnostic tool, and may provide insight into factors that affect parental responses to exome sequencing. Responses to microarray testing are nuanced and variable depending on the particular situation, though reported reactions suggest that the majority of parents perceived utility of microarray results even when a definitive genetic cause was not identified and medical management was not changed (Reiff *et al.,* 2015). Parents have also demonstrated flexibility and resilience in accommodating new information (Wilkins *et al.,* 2016). In qualitative studies, parents articulated dimensions of perceived utility including relief and fulfillment of parental responsibilities even when results were uncertain, with some parents accepting uncertainty as an inherent component of new technology (Reiff *et al.*, 2012; Hayeems *et al.,* 2016).

Early studies of parental attitudes towards whole exome sequencing have generally drawn the same conclusions, as parents report overall satisfaction with the test, despite varying degrees of frustration surrounding uncertainty and difficulty rearranging previous beliefs about the cause of their child's illness (Krabbenborg *et al.*, 2016). Parents have also expressed a desire to know as much information as possible, including variants of uncertain significance and secondary findings, and may actually request information that providers are more reluctant to share (Middleton *et al.,* 2016**)**. Furthermore, parents who were interviewed as part of a qualitative study of 25 parents of

children with rare diseases shared that they have drawn upon their ability to cope with previous health problems as evidence that they can adapt to new health threats (Sapp *et al.,* 2014). While these findings do not deny the emotional and informational weight of exome sequencing results and the importance of approaching these conversations thoughtfully, they provide evidence of parental capacities to cope with complex and uncertain situations.

In light of parental desire for diagnostic information, studies have aimed to identify areas where patient and provider informational priorities have differed when conceptualizing genetic testing options. A survey of 199 genetic counselors and 152 women who had undergone fetal microarray testing, found that genetic counselors and patients prioritized information differently, with counselors placing greater emphasis on information about testing logistics and potential limitations. In this study, surveyed patients prioritized the importance of information about the severity and prevalence of diseases that could be detected, and guidance about decisions that other couples have made in similar situations (Walser *et al.,* 2015). Patients often report a desire for information about all possible outcomes, and in an effort to satisfy this need counselors may demonstrate a tendency to provide an excess of information about their clinical rationale and population level statistics. This strategy was illuminated in a study of 101 prenatal genetic counseling sessions, in which clinicians emphasized the ability of the test to detect pathophysiology and numerical risk figures, while patients were primarily focused on creating an individualized picture of the meaning of the result and managing vulnerability attached to being labeled as "at risk" (Hunt *et al.,* 2005). Furthermore, these authors concluded that patient understanding and information recall was not

comparatively better after counseling sessions that were more dense in information provision.

These questions have also been explored in the context of pediatric exome sequencing. A recent study assessed informational needs of parents throughout the testing process for their children from consent to results disclosure. Patients reported feeling that discussion included too much information and medical jargon, and did not address the potential impact of results on their daily life and care plans for their child (Krabbenborg *et al.*, 2016). Additionally, parents reported reluctance to broach their concerns about these issues, suggesting that they could have benefitted from a more tailored and interactive protocol. These findings were echoed in a study of exome result disclosures, in which patients were most engaged during discussions about how the results would or would not change medical management (Walser *et al.,* 2017). Decisions surrounding the approach to information prioritization and communication during informed consent for exome sequencing may be influenced by counselors' perception of their ability to manage uncertainty and communicate effectively, as well as perceptions of clients' ability to understand and accept results. Exploration of these relationships may help to clarify areas in which patient and provider communication strategies can become better aligned.

Conceptual Framework and the Theory of Motivated Information Management

The proposed conceptual framework for this study (Figure 1) draws inspiration from the information provider perspective of the Theory of Motivated Information Management. The Theory of Motivated Information Management describes an interactive

process undertaken by information seekers and providers in which expected outcomes of communication and perceived efficacy are evaluated to develop an information sharing strategy (Afifi & Weiner, 2004). For the purpose of this study the provider perspective will be considered, specifically in relation to the role of perceived efficacy in mediating decision making about which and how much information to share. Perceived self-efficacy is a widely referenced concept in psychology, and has been defined as a person's belief in their ability to succeed in ways that allow them to have influence over events that affect their life (Bandura, 1997). This study will focus on two components of efficacy described in the Theory of Motivated Information Management, communication efficacy and target efficacy, as they have been shown to have significant independent effects on information management decisions in previous studies (Fowler & Afifi, 2011).

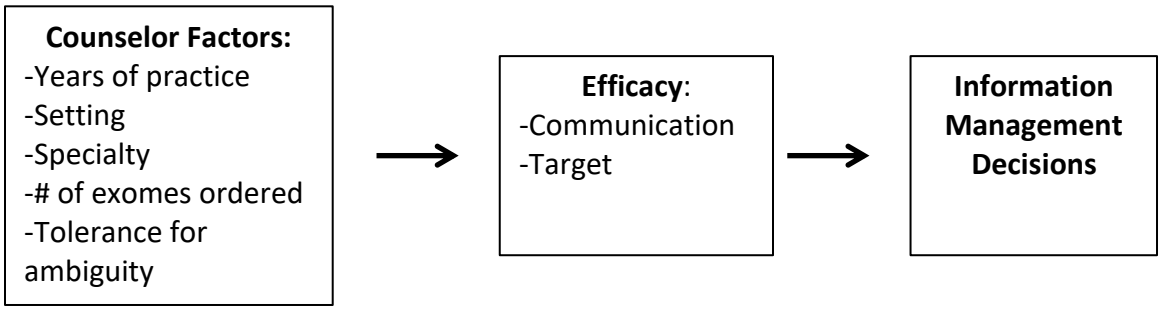

Figure 1.1: Framework Adapted from the Theory of Motivated Information Management

Communication efficacy refers to an individual's judgment of his or her ability to convey requested information effectively. Higher levels of communication efficacy have been shown to be significant predictors of the decision to seek health history information from family members in multiple studies of familial communication (Hovick, 2014; Fowler & Afifi, 2011). Intervention studies suggest that measures of communication self-efficacy can be manipulated. A study of self-efficacy among 181 physicians who underwent a patient-centered communication training program, found that scores of self-

efficacy in communication with patients and colleagues significantly increased following the intervention and that this gain in self-efficacy was stable when reassessed at six months (Norgaard *et al.,* 2012). The observed roles of communication efficacy in influencing communication suggest that interventions like the training program aimed to increase communication efficacy in both clients and counselors may facilitate more complete information sharing (Hovick, 2014).

Target efficacy refers to the provider's perception of the information seeker's ability and willingness to manage the information once it has been shared (Afifi & Weiner, 2004). Previous studies utilizing the Theory of Motivated Information Management have hypothesized that higher perceptions of target efficacy among information providers facilitate more direct styles of information sharing. One such study of partner discussions surrounding sexual health found that perceived target efficacy mediated the relationship between negative emotions and decisions to seek information, supporting a strong role for efficacy assessments in this model (Dillow & Labelle, 2014). The current study will aim to further this type of research by exploring whether efficacy assessments affect decisions about the nature of information sharing when consenting patients to exome sequencing.

Genetic counselor factors included in the model were selected to explore whether there are systematic differences in information prioritization among counselors with differing baseline characteristics and lived experiences with exome sequencing. Ongoing experience with exome sequencing has been shown to influence the way that counselors approach the informed consent process over time (Bernhardt *et al,* 2015). Exposure to genomic sequencing has also been predictive of knowledge and understanding of the

risks and benefits of testing, though time in practice or setting were not significantly associated with these outcomes (Boland *et al,* 2015). This finding suggests that other factors aside from years of practice and employment in an academic setting may be more strongly related to comfort approaching genomic sequencing. For example, genetic counselors working in the field of pediatrics are significantly more likely to have ordered clinical exome sequencing than those in other specialties like prenatal and cancer genetics (Machini *et al,* 2014). In order to further characterize which factors contribute most significantly to information provision decisions the current study will include years in practice, setting, specialty, and number of times ordering whole exome sequencing.

Previous research has also aimed to examine whether baseline personality characteristics influence the process and outcomes of genetic counseling. One such characteristic, tolerance for ambiguity, refers to an individual's level of comfort with ambiguous situations. While previous studies relating tolerance for uncertainty to genetic testing uptake have shown that low tolerance for uncertainty may act as a motivator to pursue testing, this association may differ for exome sequencing due to the inherent uncertainty associated with the technology. In exploring this relationship, a study of research participants' intentions to receive genomic sequencing results found that those with a lower baseline tolerance for uncertainty were less likely to seek medically non-actionable results (Tabor *et al.,* 2015). The current study will explore whether tolerance for ambiguity influences information sharing strategies when considered from the counselor perspective. As illustrated in the conceptual framework, these factors may interact to influence efficacy assessments which in turn mediate decisions about information management.

Methods: Best Worst Scaling

In order to determine how efficacy interacts with counselor information management decisions, it is important to accurately characterize the ways that counselors prioritize information when presented with complex genetic testing and limited time with patients. Researchers have asked counselors to describe what information they consider most salient, though stated preferences may not match clinical reality. A study that compared counselor-reported information priorities to transcripts from 101 prenatal counseling sessions found that counselors rarely include all of the information that they plan to share (Hunt *et al.*, 2005). This finding illuminates the need for alternative methods to direct questioning when attempting to elicit counselor information management decisions.

While traditionally designed for use in product development and market research, best worst scaling (BWS) has been widely applied in healthcare settings, primarily in studies to determine patient's priorities in decision-making surrounding risks and benefits of experimental treatments (Cheung *et al.,* 2016; Peay *et al.,* 2014). Best worst scaling experiments aim to elicit values that are not observable to researchers by asking participants to weigh the relative importance of factors by repeatedly selection the 'best' and 'worst' attributes from a series of choice sets (Louivere *et al*., 2013). Recently, they have been used as part of a shift to more patient-centered assessments of healthcare that focus on the whole experience rather than medical outcomes alone (Ryan *et al,* 2008). BWS studies provide more information than traditional ranking methods by collecting data about the least favored attributes and eliminating the need for participants to discriminate among attributes ranked in the middle (Erdem & Rigby, 2013).

Random Utility Theory guides the underlying premise of best worst scaling experiments. This theory asserts that people make decisions about their preferences based upon a latent construct labeled "utility", though they cannot access this construct consciously (Thurstone, 1927; McFadden, 1974). Decisions relating to this construct have systematic and random components, so identified patterns in selections among choice sets containing different combinations of attributes can be used to predict how the probability of a given choice changes when different options are presented (Louviere *et al,* 2013). This model characterizes the factors influencing random variability in decision-making that can help to identify which attributes truly hold the most value. In this study, BWS will be used to measure how genetic counselors prioritize elements of the informed consent process for pediatric clinical exome sequencing.

Another conjoint analysis method, Discrete Choice modeling, was also considered during the development of this study. Discrete choice experiments involve selecting salient attributes of a product or treatment, each with multiple levels of importance, and then creating random combinations to create distinct profiles that the participant must choose between (Coast *et al,* 2011). The process of selecting one set of random combinations of attributes over another set forces the participant to activate decision-making heuristics that they may not be able to explain directly. Despite methodological differences, BWS and Discrete Choice are both derived from the same underlying theory and have been shown to generate the same relative preference weights in an empirical comparison (Potoglou *et al.,* 2011). While this suggests the validity of both methods, the cognitive processing involved in each may differ making a certain method more suitable to particular research questions. In a study comparing the two methods, participants were

asked to talk aloud throughout their decision-making process. These authors found that there was stronger evidence for the use of "trading", or comparing two alternatives, during the Discrete Choice Experiment, though participants felt that the BWS exercise was less cognitively and ethically burdensome (Whitty *et al,* 2014). BWS was selected for this study because Aims 2 and 3 would be best addressed by generated a ranking of prioritized counseling elements. Additionally, the attributes of interest were not conducive to division into levels and all elements are independently essential to obtaining informed consent.

Best worst scaling has been applied to evaluate preferences for healthcare provision using input from healthcare providers, patients and the general population (Cheung *et al.,* 2016). In the context of genomics, BWS has been used to assess physicians' perceived barriers to implementing personalized medicine (Najafzadeh *et al.*, 2012). In this study, 197 physicians, mostly primary care doctors, participated in a BWS experiment ranking the importance of factors influencing the decision to incorporate new genomic technology into their clinical practice. They found that participants most strongly considered the degree to which genetic testing is available and accessible. Appropriate training and clear professional guidelines were also highly valued (Najafzadeh *et al.*, 2012). Another BWS study explored genetics professionals' opinions for prioritizing and allocating resources to genetic testing. These authors found that participants prioritized tests with high clinical utility, meaning those with available options for treatment or prevention), followed by tests for conditions with high prevalence in the target population (Severin *et al.,* 2013). While these studies demonstrate the utility of best worst scaling in eliciting preferences from both patients

and healthcare providers, this method has not yet been applied to assessing priorities within the counseling session from the provider perspective. Understanding the choices that genetic counselors make when faced with complicated discussions in a limited time may help to identify areas that contribute most to feelings of discomfort surrounding counseling for exome sequencing.

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PART 2: MANUSCRIPT 1

Challenges to Informed Consent for Genomic Sequencing: a Systematic Literature Review

Abstract

Despite enthusiasm surrounding genomic sequencing as a clinical diagnostic and research tool, professionals and patients have voiced trepidation about the breadth of results and the uncertainties inherent to this technology. These concerns are particularly relevant to the process of consenting individuals to undergo sequencing. Yet the specific challenges and whether they may pose barriers to informed consent have not been well delineated. To address this gap, we conducted a systematic literature review to generate an inventory of evidence-based challenges to informed consent for genomic sequencing. A search of the peer-reviewed literature in PubMed, Scopus, Web of Science, EMBASE and Cochrane databases yielded 294 distinct abstracts. Abstracts were eligible for inclusion if published from January 1, 2010, to February 28, 2017, written in English, and reporting quantitative or qualitative primary data from patients, research participants or professionals in a research or clinical setting. Eleven papers met our inclusion criteria, and qualitative meta-analysis of data across studies yielded 17 distinct challenges. The three most common challenges were: conveying the possibility of secondary findings; communicating the limitations of sequencing; and prioritizing the abundance of information. The results of our meta-analysis identified barriers to effective patient-centered communication that can be used to inform development of interventions to enhance the effectiveness of professional endeavors to consent individuals to genomic sequencing. Next steps following the systematic review may include assessment of the priorities among these consent challenges and strategies to address them.

Introduction

Genomic sequencing, primarily exome sequencing, has increasingly been incorporated into clinical practice and research studies to identify disease-causing and risk-modifying variants throughout the genome. While there is much enthusiasm about the diagnostic potential of this new technology, concerns surrounding its integration have been voiced by clinicians, researchers and patients (Biesecker & Green, 2014; Farwell *et al.,* 2014; Yang *et al.,* 2014; Boland *et al.,* 2015; Middleton *et al.,* 2016). The breadth of sequencing represents a paradigm shift from traditional genetic testing that has targeted specific genes based on phenotype and familial risk assessment, as variants may now be identified independently of clinical indications (Hooker *et al.,* 2014; Ayuso *et al.,* 2013). The wide scope of possible results due to evolving methods for data interpretation poses particular challenges to achieving informed consent. Thus, an evidence-based understanding of which elements of the informed consent process are most challenging for patients to deliberate can help providers seek opportunities to improve their approach to patient engagement and the obtainment of meaningful consent.

Broadly, informed consent for sequencing requires an understanding of the types of findings that may arise and the plan for managing and disclosing these results (Presidential Commission for Bioethics, 2012, 2013; van El *et al.,* 2013). Despite calls for the development of best practice standards, considerable heterogeneity remains in the specific content and level of detail provided by genetic counselors and practitioners when obtaining consent (Fowler *et al.,* 2017). For example, content analysis of consent documents from nine exploratory sequencing studies revealed evidence for significant variability in the descriptions of risks and benefits and in the categorization of potential

result types (Henderson *et al.,* 2014). In addition to the wide range in content and detail, a study of self-reported pre-test counseling practices demonstrated that the communication style and length of time in which providers obtain consent were also highly variable (Arora *et al.,* 2016).

As genomic sequencing enters clinical care more broadly, healthcare professionals across disciplines have an opportunity to play a critical role in deliberating patient psychosocial and informational needs as part of the informed consent process. Efforts to achieve informed choice will require attention to communication and counseling strategies (Austin *et al.,* 2014, deHaes *et al*. 2009). Despite experience consenting patients and parents of affected children to genetic testing, commentators have recognized the challenges faced by genetic counselors and researchers in communicating the complexity and uncertainty of potential results from genomic sequencing (Kost *et al.* 2017; Roche *et al.,* 2015). Concurrently, patients and participants approach testing decisions with a wide range of concerns surrounding the psychosocial impact of potential results and worries about privacy and genetic discrimination (McGowan *et al.* 2013; Robinson *et al.* 2016). Frustrations may arise when the consent process does not adequately address these decisional factors. Specifically, parents of affected children have expressed a need for increased emphasis on discussion of ways in which potential results may influence treatment and daily life (Rosell *et al.* 2016; Krabbenborg *et al.* 2016).

A systematic characterization of data from both the patient and counselor research literatures is key to understanding, and ultimately improving, the consent process for genomic sequencing. We carried out a systematic review of the literature that aimed to:

(1) characterize the nature and scope of challenges to the informed consent process as experienced by healthcare provides, researchers, patients and genomic study participants; (2) conduct a qualitative meta-analysis of the challenges inventoried; and (3) contribute evidence to guide future studies on barriers to informed consent. Determining the state of the science on challenges from multiple perspectives can inform the training and practice of healthcare providers to improve the effectiveness of informed consent for genomic sequencing.

Methods

Search Strategy

A comprehensive search of the electronic literature from January 1, 2010, to February 28, 2017, was conducted in PubMed, EMBASE, Scopus, Web of Science and Cochrane databases using the following combinations of key search terms (1) ("genome sequencing") OR "exome sequencing") OR "next generation sequencing") AND "informed consent"; and (2) ("genome sequencing") OR ("exome sequencing") OR "next generation sequencing"))) AND "genetic counseling") AND "barriers". All generated citations were collected and imported into EndNote for review.

Inclusion and Exclusion Criteria

Peer-reviewed papers were eligible for inclusion if they were: (1) written in English; (2) published in 2010 or later; (3) quantitative or qualitative studies containing primary data from patients, research participants or healthcare providers; and (4) pertaining to the informed consent process for genomic sequencing in a research or clinical setting.

Abstracts that did not meet inclusion criteria were classified into exclusion categories prior to full manuscript review. Exclusion categories included papers that were: (1) published prior to 2010; (2) pertaining to prenatal testing or newborn screening; (3) ethics perspectives or thought pieces; (4) guidelines or policy statements; (5) review papers; (6) molecular technology or diagnostic case studies; (7) regarding other types of genetic testing; and (8) Miscellaneous – i.e. non-English language, excluded study type, not relevant to informed consent, post-mortem testing.

Evaluation Method

All abstracts were reviewed by the first author and classified into exclusion categories. Manuscripts that were not excluded during the first round of evaluation were obtained and reviewed in full to produce a final list of studies that met all inclusion criteria. Any ambiguity was reconciled between the authors.

Quality Scoring

Quality was evaluated through utilization of an appraisal tool adapted from QualSyst by Paul and Colleagues (Kmet *et al.,* 2004; Paul *et al.,* 2015). All studies were evaluated on eight universal quality items assessing: clarity of objectives; study design; context; sampling strategy; participant selection; conclusion; and data collection/analysis. There were four additional items specific to study type; two were applied to qualitative studies and two were applied to quantitative studies. Mixed-methods studies were evaluated for all four additional items. Each item was assigned a score from 0-2 where 0=no, 1=partial and 2=yes. Scores were totaled and divided by the maximum possible score of 20 (24 for mixed methods studies) and multiplied by 100 to generate a final quality rating. The minimum threshold for selection into the review was sixty-five, as this

value is between a liberal cut-point of 55 and a conservative cut-point of 75, as described by QualSyst (Kmet *et al.,* 2004).

Data Extraction

Study characteristics extracted included: study type; country; study context (research or clinical setting); target population; sample size; and specific aims. Challenges to informed consent were first extracted verbatim, and redundancy was eliminated through the merging of synonymous items. Qualitative meta-analysis of findings across studies yielded the challenges that arose with greatest frequency.

Results

Study Selection and Characteristics

The systematic literature search generated 294 distinct abstracts after duplicates were removed. All abstracts were reviewed completely and evaluated for inclusion criteria and exclusion category. Following the first round of evaluation, 252 papers were excluded (reasons for exclusion are detailed in Figure 1**)**. The majority did not meet inclusion criteria for study type because they were ethics commentaries (n=73, 24.8%) and molecular studies or individual case reports (n=70, 23.8%). The remaining 42 papers were obtained and evaluated in full.

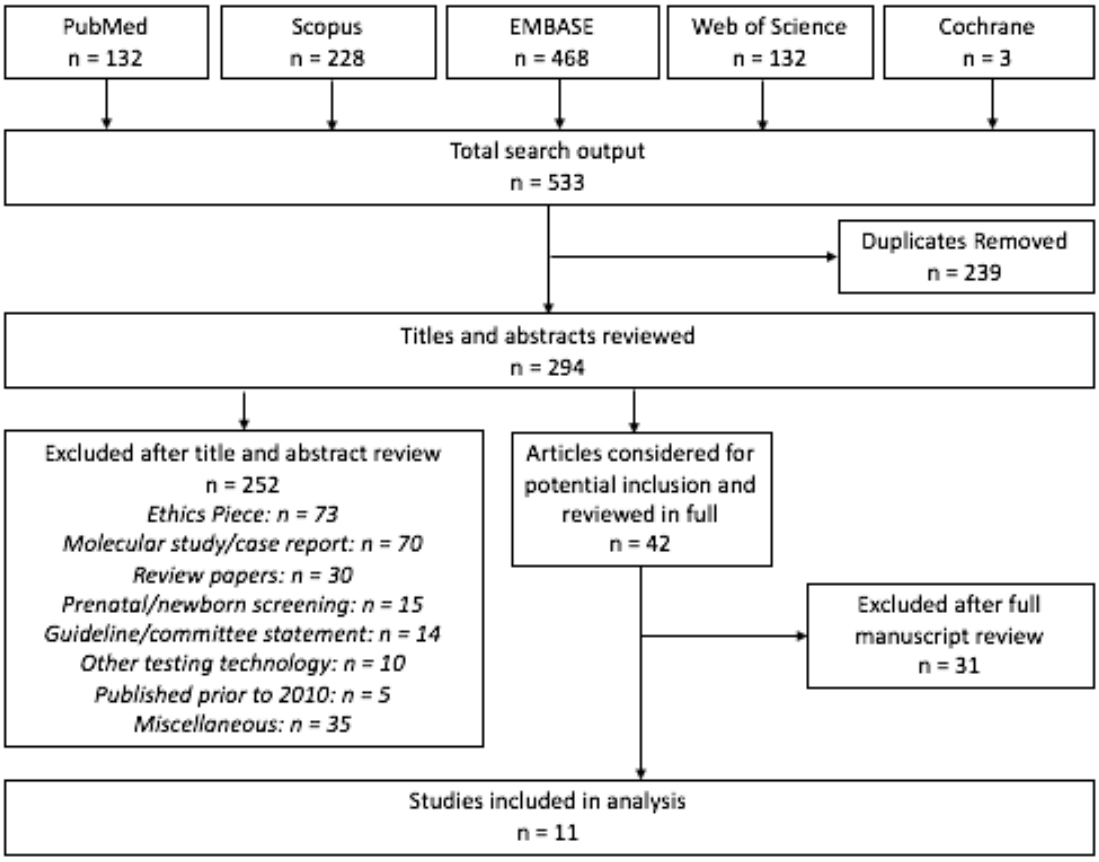

Figure 2.1: Systematic literature search flow.

After final deliberation among the authors, eleven studies were eligible for inclusion in the analysis (Table 2.1). Of these eleven studies, the majority of these were qualitative in design (n=8, 72%); two were quantitative, and one employed a mixed-methods approach. Clinical and research contexts were represented equally, with four studies exploring the informed consent process in a clinical setting, four in a research setting, and three targeting both clinical and research contexts. The majority of studies were conducted in the United States, with one study from Canada and two from the Netherlands**.** Quality scores for the included studies ranged from 70-90, with a mean score of 80. All quality scores were above the predetermined threshold of 65**.** Characteristics of the included studies are summarized in Table 2.1.

First Author (year)	Country	Context	Population	Study Type	Aim(s)	Quality
1. Appelbaum (2014)	USA	Research	Researchers (282), participants (20)	Mixed Methods	Understand views about options for returning incidental findings	75
2. Bergner (2014)	USA	Research	Research participants (15)	Qualitative	(1) Explore theoretical barriers to consent (2) Understand experienced consent process	90
3. Bernhardt (2015)	USA	Clinical; Research	Genetic counselors, coordinators (29)	Qualitative	Describe the content and process of obtaining consent for clinical sequencing	90
4. Krabbenborg (2016)	The Netherlands	Research	Parents of affected children (15)	Qualitative	Gain insight into needs of parents' of children with neurological disorders	70
5. Levenseller (2014)	USA	Clinical	Professionals (20), parents (20), adolescents (7)	Qualitative	(1) Assess views of pediatric patients, parents and professionals (2) Develop a responsive consent process	75
6. Li (2016)	Canada	Clinical	Parents of affected (15)	Qualitative	Explore parents' decisional needs for WES	85
7. Machini (2014)	USA	Clinical; Research	Genetic Counselors (221)	Quantitative	(1) Identify barriers to implementing WES (2) Report current practice systematically	90
8. Oberg (2015)	USA	Research	Parents of children with and without cancer (35)	Qualitative	Investigate parental preferences for informed consent and result return	70
9. Rigter (2014)	The Netherlands	Clinical	Professionals (11), observed counseling (3) sessions (3)	Qualitative	(1) Assess how professional experts view current informed consent practices (2) Understand patient experiences	75
10. Tolusso (2016)	USA	Clinical	Parents of children who had WES (53)	Quantitative	Assess perceived and actual understanding of WES among parents who consented	75
11. Tomlinson (2016)	USA	Clinical; Research	Genetic counselors, coordinators (29)	Qualitative	Identify unique issues associated with informed consent for WES	85

Table 2.1: Characteristics of included studies.

The eleven studies included a total of 778 participants with a range of 15-35 participants in the qualitative studies and 53-302 in the quantitative and mixed-method studies. A wide range of perspectives was captured in the included studies. Five studies targeted recipients of genetic services, including research participants and parents of children who underwent genomic sequencing, while four addressed the experience of healthcare professionals and experts in the field of genetic research. Two studies surveyed individuals from both groups. Some focused specifically on the informed consent process, while others addressed informed consent as part of a larger exploration of the implementation of genomic testing.

Challenges

Despite the wide range of contexts and populations captured in the included studies, themes in the reported challenges to the informed consent process emerged repeatedly. Following synthesis and meta-analysis of the extracted challenges, a list of

17 challenges was generated. These items are summarized in Table 2. The most prevalent challenges were: (1) conveying the possibility for secondary findings (n=8, 72.7%); (2) communicating limitations to the diagnostic potential of sequencing (n=7, 63.6%); (3) prioritizing the abundance of information in the consent session and form (n=6, 54.5%); and (4) working effectively within time constraints of the counseling session (n=6, 54.5%). Other reported challenges referenced logistical aspects of the testing process, including insurance coverage, result interpretation, and privacy protection.

Challenge	Number of Studies	Proportion (%)	Studies
Conveying the possibility for secondary findings and options for return of these results	8	72.7	1,2,5,6,7,8,9,10
Communicating limitations to the diagnostic potential of testing	7	63.6	2,3,5,7,9,10,11
Prioritizing the abundance of information – "information overload"	6	54.5	1,3,4,5,6,7
Working effectively within time constraints of the counseling session	6	54.5	1,2,3,5,7,11
Addressing uncertainty about the impact that results could have on treatment and daily life	5	45.5	2,3,4,8,11
Tailoring consent to specific indication, context and health literacy	5	45.5	3,6,8,10,11
Adequately explaining complex technology	5	45.5	2,7,9,10,11
Variant interpretation is complicated and still being developed	3	27.3	2, 5, 10
Reviewing possible implications for other relatives	3	27.3	1,3,7
Conveying risks to privacy associated with data sharing	2	18.8	1,8
Explaining the potential for insurance discrimination	2	18.8	5,9
Discussing uncertainty surrounding the broad scope of possible results	2	18.8	3,10
Recognizing when motivations for a diagnosis may overshadow considerations of risk	2	18.8	2,5
Managing the roles of children and multiple family members in testing decisions	2	18.8	5,11
Developing a plan for re-contact and evolving variant interpretation	1	0.9	5
Explaining the possibility of obtaining a variant of uncertain significance	1	0.9	7
Determining cost and insurance coverage	1	0.9	7

Table 2.2: Challenges to obtaining informed consent for genomic sequencing.

Discussion

This systematic review identified seventeen distinct challenges to the informed consent process for genomic sequencing across clinical and research settings. There was a striking degree of agreement in both the patient and provider literatures regarding the

most prevalent challenges, suggesting consistency in the elements of informed consent that influence perceived barriers to the implementation of sequencing. The results of this review highlight the importance of refining both the content and process of consent in order to facilitate patients' ability to make an informed choice about testing.

Notably, uncertainty emerged as a major theme captured by nearly all of the reported challenges. Uncertainty pervades genomics, and communicating the fundamental uncertainties surrounding the benefits and limitations of testing is essential to obtaining meaningful informed consent (Biesecker *et al.,* 2015; Brenner *et al.,* 2009). The role of uncertainty in the results of this review reflects the difficulty experienced by both patients and providers in approaching the consent process when the scope and utility of potential sequencing results is fundamentally uncertain. Though healthcare providers cannot eliminate the uncertainty inherent to the technology, exploring its many sources and dimensions may help the recipients of genomic sequencing mitigate their perceptions and act on the results as appropriate (Han *et al.,* 2017).

The relative significance of the reported challenges can be evaluated based on their prevalence and the degree to which they influence patients' ability to make an informed choice about testing. An informed choice has been defined as "one that is made based on relevant knowledge, consistent with the decision-maker's values and behaviorally implemented" (Michie *et al.,* 2002; Marteau *et al.,* 2001). Under this definition, essential elements of the informed consent process are those that capture key aspects of testing related to patient attitudes and beliefs. The two most frequently acknowledged challenges fall into this category, as candidates for sequencing must evaluate their understanding of secondary findings and testing limitations in the context

of their health care goals. Clinicians and researchers have a responsibility to engage in deliberations about these elements that explore patient values such as desire for information and tolerance of risk.

A second category of challenges incorporates elements of consent that may facilitate patient decision-making, but are not fundamental to reaching an informed choice. These include possible implications for relatives and changes to daily life. Though discussion of elements in this category may not be prioritized in written consent documents, the results of this review demonstrate that these aspects of testing are important to patients and to research participants. Emphasizing these aspects of testing may help to engage patients in collaborative deliberation that is focused on relevant and concrete outcomes of sequencing.

Notably, both patients and providers reported feeling overwhelmed by the volume of detailed technical information. This finding is consistent with communication studies demonstrating that genetic counseling sessions are often dominated by biomedical information, despite evidence that information sharing strategies lower in counselor verbal dominance and higher in active exchange facilitate improve understanding and satisfaction (Paul *et al.,* 2015; Roter *et al.,* 2006; Turbitt *et al.* 2017). Taken together, the data suggest that streamlining the amount of information discussed during the consent process would allow for more active deliberation of the testing aspects that are most relevant to patient decision-making.

The review also identified a number of procedural and administrative challenges, including time constraints on the counseling session and complications surrounding cost and insurance coverage. Addressing these challenges at an institutional level will allow

healthcare providers to focus on providing patients with a sufficient understanding of essential elements of sequencing so that they are able to make an informed choice consistent with their values. The results of this review provide a framework for characterizing challenges to the informed consent process for genomic sequencing and prioritizing which challenges to address.

Study Limitations

The search parameters yielded studies capturing a wide range of perspectives and contexts, providing a comprehensive look at the state of informed consent for sequencing. However, it is still possible that relevant sources were overlooked by the search, particularly those that referenced informed consent as a secondary focus. Relevant data may also have been missed due to the exclusion of non-English language papers and thought pieces emphasizing ethical arguments surrounding consent. We also chose to exclude papers regarding informed consent for other types of genetic testing, though these may have contained applicable data. Additionally, the small sample size of many of the included studies introduces potential bias, as they do not necessarily represent the views of a larger target population. Furthermore, studies that focused on the experience of early adopters of sequencing may not accurately reflect the current state of the field. Though all of the included studies met the predetermined quality threshold, the heterogeneity of study methods could impact the validity of the overall results of the review.

Implications for Research and Practice

There are many challenges inherent to both the content and process of obtaining informed consent for genomic sequencing. In developing more effective consent

protocols, clinicians and researchers should first focus on addressing challenges that are essential to patients' ability to make an informed choice by ensuring understanding of the potential result outcomes and limitations of testing. Providers can then work towards incorporating more complete secondary information as needed for patients making a testing decision. A tailored, stepwise process of this nature is consistent with proposed models of tiered consent that advocate for the communication of essential information followed by variable relevant information as needed to facilitate individualized patient understanding and informed choice (Bradbury *et al.,* 2015; Bunnik *et al.,* 2013).

Formalizing practices of providing less biomedical information and encouraging more dialogue about individually relevant aspects of testing could help to further develop a more effective approach to informed consent (Bernhardt *et al.,* 2015; Wynn *et al.,* 2016). Additionally, providers should take advantage of opportunities to directly address sources of uncertainty throughout the consent process. This focus could potentially mitigate negative effects of discomfort associated with uncertainty and help patients to reframe uncertainty more positively as a source of hope (Biesecker *et al.,* 2015).

This systematic review provides a foundation for future studies investigating challenges to implementing genomic sequencing in research and clinical care. Future research could aim to design and test consent protocols that focus on active deliberation with limited technical information. It would also be valuable for researchers to examine differences in provider and patient perspectives more fully, as this review found a large amount of agreement about general challenges. The results of this review directly contributed to the development of a best worst scaling experiment designed to assess genetic counselors' perceptions of the greatest challenges to the informed consent process

among those identified from this review. This line of research will help to clarify how the challenges reported in the literature influence consent practice currently, and to improve training to target these issues specifically.

Conclusion

This systematic literature review identifies 17 distinct challenges to the informed consent process for genomic sequencing as experienced by patients and healthcare providers. The results highlight the importance of addressing sources of uncertainty; engaging in dialogue about elements of testing that are essential to informed choice; and streamlining the presentation of complex technical information. This characterization of challenges to the informed consent process for genomic sequencing provides a foundation for future research as well as a framework for the ongoing development of consent practice and training for practitioners.

Acknowledgements

We would like to thank Barbara Brandys, NIH librarian, for her help in designing the search terms.

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PART THREE: MANUSCRIPT 2

Challenges to Informed Consent for Exome Sequencing: a Best Worst Scaling Experiment

Abstract

As exome sequencing expands as a diagnostic tool, patients and providers have voiced concerns about the breadth and scope of potential results. Particularly, genetic counselors perceive challenges to prioritizing complex information during informed consent sessions. This study aimed to understand how genetic counselors approach the consent process and weigh the relative importance of its many components. Best-worst scaling methodology was used to characterize how genetic counselors prioritize essential elements of informed consent specific to exome sequencing. The development of a best-worst scaling experiment was informed by a systematic review of the literature and two focus groups. Choice sets were created using a balanced incomplete block design, where participants selected the most and least important attribute in each choice set. Mediation analyses were used to assess whether responses were associated with previous experience ordering exome sequencing, perceived efficacy in consenting patients, and counselors' tolerance for ambiguity. An online survey was distributed to all full members of the National Society of Genetic Counselors and completed by 342 recipients. Data were analyzed using mean best-worst scores to summarize the number of times each attribute was selected as most and least important. Ranking of best-worst scores suggests that genetic counselors prioritize collaborative decision-making, assessing patient understanding and managing expectations for results, with the least emphasis placed on discussing technological complexities. Stratified analyses by paired t-tests found that counselors with more experience ordering exome sequencing, and those reporting higher

perceptions of patients' ability to manage information were significantly more likely to prioritize discussion of variants of uncertain significance ($p<0.05$). Results convey counselors' prioritization of individual patient needs for obtaining informed consent for exome sequencing, and that professional characteristics and attitudes may influence preemptive discussion of uncertain results. Future studies are needed to determine how counselors' consent practices exhibit these priorities.

Introduction:

Since its introduction as a research and more recently, a clinical tool, exome sequencing has been met with both enthusiasm and trepidation. Despite the excitement surrounding diagnostic potential, there has been much debate about how to manage secondary findings, evolving result interpretation, and variants of uncertain significance (VUS) (Bertier *et al.,* 2016; Green *et al.,* 2013). Rigorous informed consent is essential to ensure that patients and parents accurately understand the limitations and potential uncertainties of genomic sequencing (Biesecker & Green, 2014, Bernhardt *et al., 2015*). Broadly, informed consent must address expected outcomes of testing including the type and likelihood of results that will or will not be returned, as well as the risks, benefits, limitations, alternatives to testing and potential implications for relatives (ACMG Board of Directors, 2013; Ayuso *et al.,* 2013).

The unpredictable nature and broad scope of potential results challenge the paradigm of traditional informed consent procedures that have been applied to more targeted genetic testing (Hooker *et al.,* 2014; Bernhardt *et al.,* 2015). Uncertainties pervade exome sequencing, as the majority of variants identified are currently classified

as VUS and lack clear-cut management recommendations (Han *et al.*, 2017; Bertier *et al.,* 2017). A lack of identification of any pathogenic variants is nuanced and generally treated as provisional given the evolving understanding of interpretation (Skinner *et al.* 2016). These challenges are particularly salient in the pediatric setting where children undergoing a diagnostic workup have the potential to learn information about risk for unrelated adult onset conditions that could profoundly influence developing self-identity (Miller *et al.,* 2017; Werner-Lin *et al.,* 2016). Current guidelines and laboratory practices provide an option for patients to opt-out of receiving medically actionable secondary findings (Kalia *et al.,* 2017; O'Daniel *et al.,* 2017). This decision must be made prior to ordering testing, and is often considered during the informed consent session. These choices can be complicated by the involvement of children in providing assent, and the possible implications for parents and relatives when trio testing is ordered (Levenseller *et al.,* 2014; Bernhard *et al.,* 2015). Furthermore, families of children affected with developmental delays and/or rare undiagnosed conditions often have high expectations for the diagnostic capability of sequencing that may inhibit their ability to fully accept the limitations of testing (Anderson *et al.*, 2016; Tomlinson *et al.,* 2016).

Most often, genetic counselors are the professionals consenting adults and parents to genomic sequencing (Machini *et al.* 2014; Egalite *et al.* 2014). They report concerns about the amount and complexity of information included in consent documents and professional guidelines which may impact how they communicate these concepts (Bernhardt *et al.,* 2015; Rigter *et al.,* 2014). Studies of communication about genetic testing have found that professional presentation of biomedical information often dominates the interaction, leading to limited patient participation (Paul *et al.,* 2015; Roter

et al., 2006). Despite clear intentions and attempts to engage patients, discussions of exome sequencing have also been dominated by provider provision of genomic education (Walser *et al.,* 2017; Levenseller *et al.,* 2015). This pattern may explain parents' reporting that pretest counseling underemphasizes discussions of the aspects of testing they value, such as how results could impact daily life (Krabbenborg *et al.,* 2016). As genetic counselors have become more familiar with informational content of genomic sequencing, there has been a reported shift towards more interactive consent sessions with lower prioritization of technical information (Bernhardt *et al.,* 2015; Wynn, 2016). This suggests that experience with exome sequencing may lead to adjusted consent strategies.

To capture the many factors that may affect the process of achieving informed consent for exome sequencing, this study was informed by the Theory of Motivated Information Management (Afifi & Weiner, 2004). This theory describes an interactive process in which information providers make decisions about communication based on assessments of the information recipient and projected outcomes of the interaction. Particularly relevant to this study are the concepts of communication efficacy, an individual's perception of their own ability to share information effectively, and target efficacy, perceptions of the recipient's willingness and ability to manage information (Afifi & Weiner, 2004). Higher levels of both concepts have been associated with greater intentions to share information directly (Hovick, 2014; Fowler & Afifi, 2011; Dillow & Labelle, 2014). This theory was used to frame a study to answer whether communication and target efficacy influence how genetic counselors prioritize elements of informed consent.

Best-Worst Scaling

To assess these relationships, information management strategies must be operationalized quantitatively. Best-worst scaling (BWS), a type of conjoint analysis traditionally used in marketing research, has recently been appropriated into health care research as a method for evaluating stakeholder priorities (Cheung *et al.*, 2016; Flynn *et al.*, 2007; Mulbacher *et al.,* 2016). BWS relies on the basic assumptions that individuals make decisions to maximize utility, and that a component of utility is not consciously accessible (Thurstone 1927, McFadden, 1974). As such, BWS aims to elicit underlying valuations by gathering data about choices made at the extreme ends of preference (Louviere & Flynn, 2010). This approach is more reliable in predicting outcomes than traditional ranking systems as it requires participants to select only the best and worst items in a series of choice sets, thereby eliminating the need to make indiscriminate choices about midrange items (Louviere *et al.,* 2007; Peay *et al.,* 2015; Edem & Rigby, 2013). Previous applications of BWS in the context of genetics research have explored perceived barriers to personalized medicine and prioritized outcomes of genetic testing (Najafzadeh *et al.,* 2011; Severin *et al.,* 2013). These authors found that healthcare providers placed the highest value on genetic tests with high clinical utility, defined as those with associated medical interventions, and tests for highly prevalent conditions (Severin *et al.,* 2013). Physicians also consider the type of testing, their training and professional guidelines when assessing the feasibility of incorporating genetic testing into their practice (Najafzadeh *et al.,* 2011). As new genomic technologies enter clinical care, BWS provides a valuable tool for understanding preferences to guide implementation and policy.

Previous research has focused on identifying the essential elements of informed consent for exome sequencing, but to our knowledge have not explored how genetic counselors prioritize these items in consent sessions with patients (Ayuso *et al.,* 2013; Presidential Commission for Bioethics, 2013). Gaining a clearer understanding of genetic counselors' approach to obtaining consent can inform the development of more standardized practices and identify potential discordance between patient and provider priorities. This study used a Best-Worst scaling experiment to understand how genetic counselors prioritize elements of informed consent when presenting options for exome sequencing in a pediatric clinical setting. The second aim was to explore the relationship between prioritization decisions and counselor factors such as experience with exome sequencing, tolerance for uncertainty, communication efficacy and target efficacy. We hypothesized that genetic counselors reporting more experience with exome sequencing and higher communication efficacy would place less emphasis on discussing the technical aspects of sequencing, and would prioritize discussions about outcomes of testing and decision-making.

Methods

Best-Worst Scaling Task Design

Consideration and design of a best-worst scaling (BWS) experiment was in accordance with standards put forth by the ISPOR checklist for conjoint analysis (Bridges *et al.,* 2011). Best-worst scaling was selected based on the exploratory nature of the research question, and the added benefit of collecting data about the least prioritized aspects of informed consent. Three types of BWS methodology have been described that

use the same underlying principles to capture differing aspects of participant choice (Louviere *et al,* 2007). Based on the current structure of informed consent components, BWS Case 1 (object case) was selected. BWS Case 1 provides information about the relative ranking of individual attributes, and does not include sublevels within each item like BWS Cases 2 and 3. Across all types of best-worst scaling studies, attributes should contribute separately to the underlying "utility" construct and must be comparable to each other (Mulbacher *et al.*, 2016; Coast *et al.,* 2012).

Attributes were proposed using evidence from the published literature as well as qualitative analysis of focus group data to encompass all relevant aspects of informed consent for exome sequencing (Bridges *et al.,* 2011). Attribute development was conducted in a two-step process, starting with the conceptual delineation of each item followed by the refinement of meaningful language (Coast *et al,* 2012). A preliminary list of seventeen attributes capturing challenges to informed consent for genomic sequencing was developed from a systematic review of the literature published from January 2010 to February 2017 (findings presented in Part 1).

Two focus groups were subsequently conducted with six genetic counselors in total, who all reported previous experience with exome sequencing. Each focus group was facilitated by the student investigator using an interview guide in conjunction with paper forms listing the preliminary attributes. Focus group participants were asked to draw upon their clinical experience to provide oral and written feedback on the preliminary elements, and to suggest additional elements that may not have been captured. Focus group participants generally endorsed the preliminary elements, and suggested removing select attributes due to redundancy and dividing one attribute that

captured two concepts into two distinct elements. These results were incorporated to devise the final list of elements.

The final list of eleven attributes was organized into choice sets using a Balanced Incomplete Block Design (BIBD) so that each attribute appears the same number of times and co-appears with all other attributes evenly (Street & Street, 1987; Louviere *et al.,* 2007). The BIBD used in this study was generated using the "support.BWS" package for R statistical software (Aizaki, 2017; other R how to). In this design, all attributes appear five times and participants are presented with eleven choice sets, each containing five items. After choice sets were constructed, the attributes were randomized within each choice set to control for potential bias from ordering effects. The order in which choice sets were presented was randomized as well. For each choice set, participants were asked to select the most and least important attribute. A sample choice set is presented in Figure 3.1.

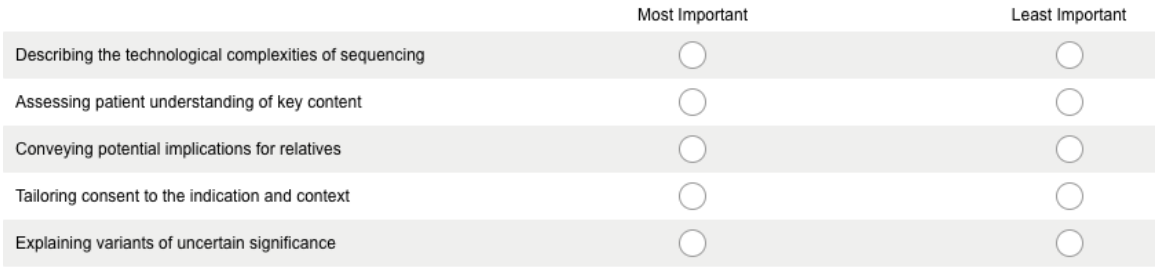

Figure 3.1: Sample choice set presenting five attributes.

Study Instrument Design

In addition to the best-worst scaling experiment, the survey assessed participant characteristics, professional experience and attitudes towards informed consent for exome sequencing. Demographic characteristics included age, gender, race and ethnicity, geographic location, years in practice, practice specialty, and experience ordering exome sequencing. Tolerance for uncertainty was measured using the modified Tolerance for

Ambiguity scale, a 7-item measure capturing the degree to which an individual is comfortable approaching uncertain situations (Geller *et al,* 1993). This scale was previously validated for use in the context of genetic testing. A 6-item knowledge check was adapted from the whole exome sequencing domain of the UNC Genomic Knowledge Scale to assess understanding of relevant basic concepts (Langer *et al.,* 2017). This scale was originally designed for a patient population; thus, it was expected that most participants would answer correctly allowing responses to be used as a validity check for the sample.

A hypothetical pediatric clinical scenario was designed to provide a standardized context for the best-worst scaling tasks. The scenario provided a general indication for pediatric exome sequencing, but did not offer detailed clinical or psychosocial information about the hypothetical patient. In line with previous work using hypothetical patients, the scenario was written to maximize verbal immediacy, the degree of direct communication between the source and receiver of information, as well as temporal proximity, the portrayal of a situation as having immediate consequences (Persky *et al,* 2007). Communication efficacy and target efficacy were assessed in the context of the hypothetical scenario with four items each rated using a 7-point Likert scale. These were modeled on instruments validated in previous studies informed by the Theory of Motivated Information Management (Hovick *et al.*, 2014; Fowler & Afifi, 2011).

Prior to initiation of the BWS experiment, attributes were presented individually and participants were asked to report the degree to which they perceived each attribute to be challenging using a sliding scale from 0 to 100. The BWS tasks required participants to select the single ‘most important’ and ‘least important’ elements of informed consent

in each five-attribute choice set. A selection had to be made before advancing to the next choice set. At the end of the survey participants had the opportunity to provide open ended feedback about their experiences with exome sequencing and completing the BWS study. The online survey was assembled and formatted using Survey Monkey. Four genetic counselors employed in a variety of settings pilot tested the instrument, and feedback was incorporated prior to survey finalization. Modifications included providing more detailed instructions before introducing the best worst scaling tasks and presenting explanations of each attribute below the choice sets in a standardized order.

Recruitment and Participants

Eligible participants were full members of the National Society of Genetic Counselors (NSGC) practicing in any specialty or setting in the United States or Canada. Previous experience ordering exome sequencing was not required. Study invitations were sent via the NSGC email listserv to over 4,040 genetic counselors, and a reminder email was sent two weeks later. Participants were offered a $10 Amazon gift card for completing the survey. Both the focus group interview study and the anonymous survey were determined to be exempt from IRB approval by the NIH Office of Human Subject Research Protection (OHSRP). The survey was assembled and distributed via Survey Monkey.

Target sample size was estimated using G*Power 3 at a significance level of 0.05 and a power level of 0.80 (Faul *et al,* 2007). Effect size was set at 0.06, a conservative estimate based on the correlation between efficacy scores and information management decisions reported in previously published studies (Fowler & Afifi, 2011; Afifi & Weiner, 2006). Based on these parameters, a target sample of 220 participants was sought

to sufficiently power the study. This target sample size is consistent with requirements for conjoint analysis (de Bekker Grob *et al.,* 2015).

Data Analysis

Best-worst scaling data was analyzed using a count based approach. In this method, the relative importance of each attribute is reported as a Best-Worst (BW) score calculated by subtracting the total number of times that the item was selected as the least important from the number of times that it was chosen as the most important (Flynn *et al.,* 2007; Peay *et al,* 2015). Total BW scores were then divided by the number of times that each attribute was available to be chosen. This generates a mean BW score for each attribute that can be used for standardized ranking. Individual BW scores were also calculated for every participant, and ranged from -5 to +5 for each attribute. Dividing the individual BW scores by five generated individual mean scores for each attribute that were then used to calculate standard errors for the overall mean BW scores. Standardized mean BW scores were rank ordered and reported with standard deviations and 95% confidence intervals.

There are a variety of methods for analysis of BWS data, this method was primarily selected because it is conducive to running stratified analyses examining one variable at a time. Additionally, standardized mean scores for each attribute can be compared to each other and variables do not need to be coded (Peay *et al.,* 2014). Despite its relative simplicity, the count-based approach has been shown to yield valid object measures comparable to those derived with more complex regression-based models such as conditional logit and linear probability (Flynn *et al,* 2007; Louviere & Flynn, 2010). Thus, this method provides valid and reliable results, but is still

conceptually accessible to the target population of genetic counselors and clinical policy makers.

Four stratified analyses were performed among groups that differed by level of previous experience with exome sequencing, tolerance for ambiguity, communication efficacy and target efficacy. Mean BW scores were generated for all attributes in each group, and two tailed t-tests were conducted to assess whether between-group differences for any of the attributes were statistically significant (Peay *et al.,* 2015). Demographic data was reported using descriptive summary statistics for the whole population and separating based on degree of experience with exome sequencing. The probability test function in Stata was used to test whether characteristics varied significantly between the two groups.

Results

A total of 375 genetic counselors initiated the survey, and 342 completed the study in its entirety. Incomplete surveys were excluded, and the 342 complete responses were used in the analysis. 97.6% of participants answered all items on the knowledge scale correctly, supporting validity of the sample. Participants reported a wide range of experience with exome sequencing; 7.6% had ordered 50 or more exome sequencing tests, 12% had ordered 30-49, 19.8% had ordered 10-29, the majority (38.6%) had ordered sequencing 1-9 times, and 22% had never ordered it. The sample was split into two groups based on experience, the ‘less experienced’ group included those who had ordered exome sequencing zero to nine times (60.8%), and 39.2% were in the ‘more experienced’ group that reported ordering sequencing 10 times or more.

Table 3.1 summarizes respondent characteristics. Some participants declined to answer select demographic questions. The majority of participants were Caucasian females who reported working primarily in a clinical setting. These demographic findings matched that of the larger membership of NSGC and the target population of genetic counselors (PSS, 2016). The sample included genetic counselors in a variety of specialties, with the largest proportion working in pediatrics (31.8%). Most of the respondents had been in practice for less than five years (62.3%). Tolerance for ambiguity (TFA) varied among the sample, but generally trended towards lower TFA with a mean score of 20.0, ranging from 7 (highest TFA) to 31 (lowest TFA). Communication efficacy and target efficacy were generally high across the whole sample, with a mean score of 6.1 and 5.0 out of 7, respectively. Scores on these two efficacy scales were not highly correlated (R=0.44).

When separated by experience with exome sequencing, there were significant differences in setting and specialty. Those in the less experienced group were significantly more likely to work in a prenatal, cancer or laboratory setting, while pediatric genetic counselors made up most of the more experienced group ($p=<0.01$). These differences were expected and are consistent with current clinical use of exome sequencing (Bertier *et al.,* 2017). There was also a statistically significant difference in perceptions of both communication and target efficacy, as counselors with more experience reported significantly higher mean efficacy scores for both domains ($p=<0.01$). There were no significant differences in tolerance for ambiguity or other demographic characteristics between the two groups.

	Total Sample (n=324)	Less Experience (n=208)	More Experience (n=134)	*P*-Value
Gender	n (%)	n (%)	n (%)	
Female	323 (94.4%)	199 (95.7%)	124 (92.5%)	0.21
Male	18 (5.3%)	8 (3.8%)	10 (7.5%)	0.13
Age				
20-29 years	191 (55.8%)	117 (56.3%)	74 (55.2%)	0.84
30-39 years	108 (31.6%)	61 (29.3%)	47 (35.1%)	0.26
40-49 years	25 (7.3%)	17 (8.2%)	8 (6.0%)	0.45
50-59 years	14 (4.1%)	10 (4.8%)	4 (3.0%)	0.41
Ethnicity				
Caucasian	313 (91.5%)	186 (89.4%)	127 (94.8%)	0.08
African American	3 (0.9%)	3 (1.4%)	0 (0.0%)	0.17
Hispanic	5 (1.5%)	5 (2.4%)	0 (0.0%)	0.07
Asian	16 (4.7%)	11 (5.3%)	5 (3.7%)	0.49
Other	5 (1.5%)	3 (1.4%)	2 (1.5%)	0.94
Years in Practice				
<5	213 (62.3%)	130 (62.5%)	83 (61.9%)	0.91
5-9	77 (22.5%	45 (21.6%)	32 (23.9%)	0.62
10-19	34 (9.9%)	22 (10.6%)	12 (9.0%)	0.63
20-29	16 (4.7%)	10 (4.8%)	6 (4.5%)	0.9
30+	2 (0.6%)	1 (0.5%)	1 (0.7%)	0.81
Geographic Region				
Northeast	93 (27.9%)	55 (26.4%)	38 (28.4%)	0.69
Midwest	106 (31%)	62 (29.8%)	44 (32.8%)	0.56
South	64 (18.7%)	37 (19.7%)	27 (20.1%)	0.93
West	58 (17.0%)	41 (19.7%)	17 (12.7%)	0.09
Primary Role				
Clinical Care	269 (78.7%)	158 (76.0%)	111 (82.8%)	0.13
Research	24 (7.0%)	11 (5.3%)	12 (9.0%)	0.18
Laboratory	45 (31.2%)	31 (14.9%)	9 (6.7%)	**0.02**
Other	7 (2.0%)	5 (2.4%)	2 (1.5%)	0.57
Speciality				
Pediatric	109 (31.9%)	28 (13.5%)	81 (60.4%)	**<0.01**
Prenatal	56 (16.4%)	48 (23.1%)	8 (6.0%)	**<0.01**
Cancer	85 (24.9%)	80 (28.5%	5 (3.7%)	**<0.01**
Other	91 (26.6%)	51 (24.5%)	40 (29.9%)	0.27
Attitude Scales	Mean (SD)	Mean (SD)	Mean (SD)	*P*-Value
Communication Efficacy	6.09 (1.08)	5.73 (1.19)	6.64 (0.52)	**<0.01**
Target Efficacy	4.98 (1.03)	4.78 (0.97)	5.32 (1.01)	**<0.01**
Tolerance for Ambiguity	20.20 (4.30)	20.30 (4.46)	19.60 (4.01)	0.13

Table 3.1: Sample characteristics for participants overall, and stratified by experience.

Prioritized Elements of Informed Consent

Before starting the best-worst scaling tasks, participants rated the degree to which they found each attribute challenging on a sliding scale from zero to one hundred. The top three most challenging elements were: “managing patient expectations for results” (mean 41.85), “assessing patient understanding” (36.39), and “describing technological complexities” (mean 34.98). “Discussing implications for relatives” was rated as least challenging (24.72).

Ranked mean BW scores with standard errors and 95% confidence intervals are presented in Table 3.2 and represented graphically in Figure 3.2. “Engaging patients in collaborative decision making” was endorsed as the most important element of obtaining informed consent (BW=0.596, SE=0.019). Participants also reported prioritizing “assessing patient understanding” (BW=0.584, SE=0.018) and “managing patient expectations” (BW=0.380, SE=0.018). The least important attributes were “discussing technical complexities” (BW=-0.812, SE=0.015) and “explaining evolving variant interpretation” (BW=-0.322, SE=0.018). “Explaining variants of uncertain significance” (BW=0.250, SE=0.014) was ranked as the midpoint, and this mean BW score was not statically significantly different from zero (95% CI: -0.034,0.02).

Attribute	Best	Worst	Total B-W Score	Mean B-W Score	Standard Error	95% Confidence Interval
Engaging patients in collaborative decision-making	1041	22	1019	0.596	0.019	(0.56, 0.63)
Assessing patient understanding of key content	1104	6	998	0.584	0.018	(0.55, 0.62)
Managing patient expectations about results	705	55	650	0.380	0.018	(0.34, 0.42)
Tailoring consent to the indication and context	298	223	75	0.044	0.021	(0.002, 0.09)
Deliberating about secondary findings	198	163	35	0.021	0.016	(-0.01, 0.5)
Explaining variants of uncertain significance	167	179	-12	-0.007	0.014	(-0.03, 0.02)
Clarifying the meaning of a negative result	182	260	-78	-0.046	0.016	(-0.08, -0.01)
Conveying potential implications for relatives	66	372	-306	-0.179	0.015	(-0.21, -0.15)
Warning for insurance discrimination	34	475	-441	-0.258	0.018	(-0.29, -0.22)
Explaining the evolution of variant interpretation	57	608	-551	-0.322	0.018	(-0.36, -0.29)
Describing technological complexites	10	1398	-1388	-0.812	0.015	(-0.84, -0.78)

Table 3.2: Attributes ranked by relative importance with total BW scores, mean BW scores, standard error and 95% confidence intervals.

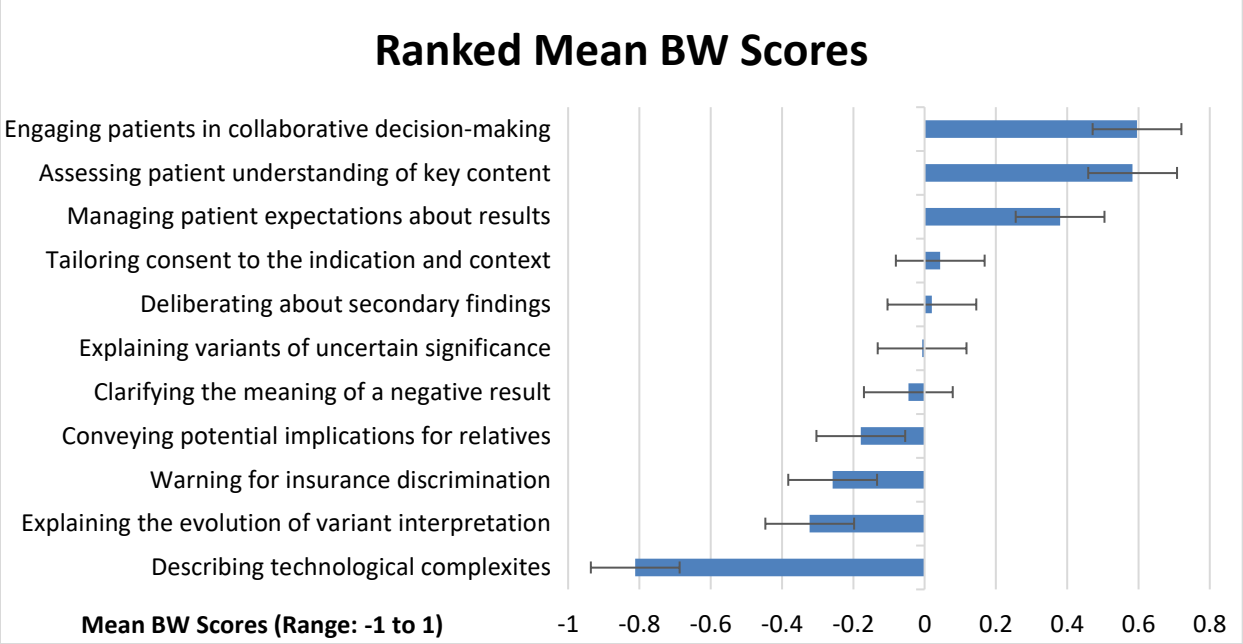

Figure 3.2: Attributes ranked by relative importance using mean Best-Worst scores. Bars represent standard errors.

Stratified BWS analyses were conducted by experience with exome sequencing, communication efficacy, target efficacy and tolerance for ambiguity. Results of the stratified analyses with p-values from two-sided t-tests are summarized in Table 3.3. Significant differences were observed for the following attributes after stratifying by

experience with exome sequencing: “explaining variants of uncertain significance” (p=0.036), “conveying implications for relatives” (p=0.002) and “clarifying the meaning of a negative result” (p=0.00013). These differences are compared in Figure 3.3. The efficacy and TFA responses were divided into low and high groups based on the mean scores for each construct. Respondents in the high perceived target efficacy group ranked “explaining variants of uncertain significance” as significantly more important than those in the low target efficacy group (p=0.036). There were no significant differences in mean BW scores after stratifying by communication efficacy or tolerance for ambiguity.

	Experience with Exome			Communication Efficacy			Target Efficacy			Tolerance for Uncertainty		
	Less Ordered	More Ordered		Low Score	High Score		Low Score	High Score		Low TFA	High TFA	
Attibute	(Mean BW)	(Mean BW)	P-Value	(Mean BW)	(Mean BW)	P-Value	(Mean BW)	(Mean BW)	P-Value	(Mean BW)	(Mean BW)	P-Value
Assessing patient understanding	0.605	0.334	0.13	0.586	0.581	0.88	0.597	0.561	0.32	0.601	0.568	0.34
Engaging patients in decision-making	0.588	0.343	0.58	0.578	0.614	0.34	0.594	0.598	0.92	0.581	0.609	0.47
Managing patient expectations	0.380	0.329	0.98	0.578	0.614	0.34	0.594	0.598	0.92	0.399	0.363	0.33
Tailoring consent to the indication	0.031	0.377	0.44	0.031	0.057	0.53	0.061	0.016	0.30	0.020	0.066	0.28
Deliberating about secondary findings	0.025	0.305	0.73	0.006	0.036	0.35	-0.001	0.056	0.09	0.001	0.038	0.27
Clarifying the meaning of a negative	0.003	0.282	**<0.01**	-0.022	-0.071	0.12	-0.033	-0.067	0.30	-0.069	-0.024	0.16
Explaining the potential for a VUS	-0.054	0.230	**<0.01**	-0.051	-0.018	0.81	-0.029	0.030	**0.04**	0.012	-0.024	0.17
Conveying implications for relatives	-0.141	0.269	**<0.01**	-0.165	-0.194	0.33	-0.162	-0.208	0.14	-0.200	-0.160	0.19
Warning for insurance discrimination	-0.278	0.361	0.16	-0.269	-0.247	0.56	-0.244	-0.281	0.33	-0.222	-0.290	0.07
Explaining evolving variant interpretation	-0.329	0.326	0.93	-0.304	-0.341	0.30	-0.340	-0.292	0.20	-0.309	-0.334	0.90
Describing the technological complexities	-0.828	0.251	0.19	-0.814	-0.810	0.89	-0.824	-0.791	0.27	-0.814	-0.810	0.90

Table 3.3: Mean BW scores compared based on experience with exome sequencing, communication efficacy, target efficacy and tolerance for ambiguity. P-values represent the results of a two-tailed t-test for the difference between two group means.

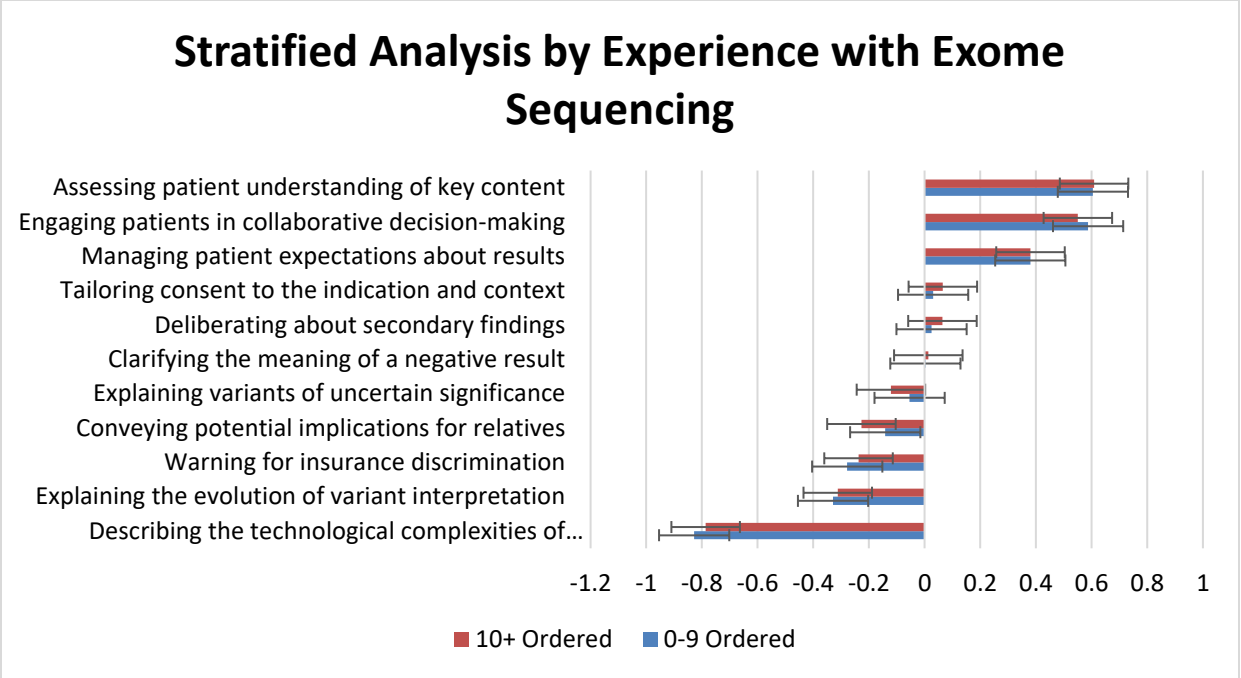

Figure 3.3: Mean BW scores compared by experience ordering exome sequencing.

Discussion

Our results suggest that genetic counselors most highly value elements of the informed consent process that facilitate patient engagement and shared deliberation. Conversely, they rank discussing complex technical information and variant interpretation as least important. These findings were consistent among counselors with and without direct experience with exome sequencing, suggesting that these intentions are rooted in professional values rather than individual experience with genomic sequencing. The observed ranking favors elements of informed consent that increase patient participation and invite clarifying questions. Because these attributes focus on understanding personal preferences for testing, the stated priorities are also congruent with the definition of informed choice as a decision that is made and implemented with sufficient knowledge and supported by individual values (Michie *et al.,* 2002).

Participants also highly rated the importance of managing expectations for potential results, an essential aspect of pretest counseling that may be challenging to convey (Skinner *et al.,* 2017).

This study provides evidence for a unified view of intentions for approaching informed consent for exome sequencing. However, more research is needed to understand how these intentions translate into practice. Observations from a recent study of exome result return clearly demonstrated providers' attempts to assess patient understanding, but found misunderstandings were not fully addressed and many of these sessions defaulted to information-heavy communication (Walser *et al,* 2017). Similarly, a study of methods used to facilitate child involvement in informed consent sessions found that most providers attempted to engage children, but did not fully utilize specific strategies such as starting the session with procedural information that is most likely to be salient to children (Miller *et al.,* 2017). Genetic counselors have a clear desire and intention to facilitate understanding and collaborative decision-making, and may benefit from training in specific communication strategies, such as teach back methods, to further implement counseling goals. These tools may be particularly beneficial when involving children or adolescents who may not be accustomed to participating in healthcare decisions (Werner-Lin *et al.,* 2016).

Another major finding was that explaining variants of uncertain significance (VUS) was rated as significantly more important among respondents with more experience ordering exome sequencing and those with higher perceived target efficacy. Questions about the interpretation and communication of VUS results has been central to debates surrounding the utilization of exome sequencing, especially given that there is

currently a higher yield of VUS results than pathogenic variants (Bertier *et al.,* 2017). Counselors with more experience ordering exome sequencing may be more acutely aware of the high probability of obtaining a VUS result, and this may motivate them to prioritize this discussion during informed consent. Along the same lines, more experience with exome sequencing may also lead to increased comfort with discussing uncertainty and providing anticipatory guidance prior to results disclosure. As part of these discussions, providers can help patients to frame VUS results in a productive manner as they may represent future possibilities for clarity and an opportunity for future partnering with the care team (Timmermans *et al.,* 2016; Walser *et al.,* 2017).

In the cancer setting, VUS results have been associated with a moderate but significant increase in patient distress (Lumish *et al.,*2017). There is also evidence that some parents have difficulty conceptualizing the meaning of a VUS in the context of microarray testing (Kiedrowski *et al,* 2015; Reiff *et al.,* 2012). Knowledge that it can be challenging for parents to understand and adapt to the finding of a VUS could explain why participants with lower perceptions of target efficacy ranked explaining the possibility of uncertain results significantly lower than those in the high target efficacy group. Genetic counselors with more experience ordering exome sequencing reported significantly higher perceptions of target efficacy, suggesting that target efficacy may mediate the relationship between experience and value placed on discussing variants of uncertain significance. While uncertainty cannot be eliminated from exome sequencing, providers have an opportunity to help patients understand differing sources of ambiguity and identify areas where they can attempt to find control in the face of uncertainty (Han *et al.,* 2017). These ideas may be particularly helpful if explored during pretest

counseling so that patients can begin to build a concept of uncertainty prior to receiving a result.

Limitations

The findings of this study are limited by the fact that many participants did not have direct experience with exome sequencing. As a result, the findings should be interpreted primarily as intentions rather than reported actions. More research is needed to understand how these intentions are implemented in practice. Despite this limitation, responses from these participants helped to identify relevant differences between groups with differing levels of experience and mirrored current uses and prevalence of exome sequencing. Additional limitations arise from the demographic homogeneity of the sample, though our respondents were highly representative of overall NSGC membership (PSS, 2016).

There could also be limitations in the ability of utilized scales to fully capture the constructs of interest. Particularly, additional heterogeneity in perceived communication and target efficacy might have been identified if more items were included in these scales. Furthermore, tolerance for uncertainty is a complex construct encompassing a variety of cognitive and emotional reactions. A number of scales have been designed, though there is an observed lack of consistency and coherence across these measures (Hillen *et al.,* 2017). The scale used in this study was selected because it has been previously validated for use with genetics professionals (Gellar *et al.*, 1993). However, we recognize that it may not have addressed the full spectrum of factors that contribute to an understanding of tolerance for uncertainty.

Despite the rigorous attribute development process, it is possible that important concepts were not captured by the included items. Inclusion of additional attributes could have provided more nuanced results. Additionally, participants could have perceived conceptual overlap or clear superiority among some of the attributes leading to difficulty in making direct comparisons. Meaning of each attribute could have been interpreted differently by individual participants, which would also have influenced responses. Future studies could gather additional information by using a similar method to survey a patient population.

Practice implications

As exome sequencing becomes more widely used, patients may benefit from an increased understanding of sources of uncertainty as well as clarification of their attitudes towards uncertainty. Acknowledgement of uncertainty should be included in the informed consent process, as uncertainty can be raised with any outcome of sequencing. Since many of the respondents had never ordered exome sequencing, the best-worst scaling task could have acted as a values clarification exercise to help participants begin thinking about what they find most challenging about exome sequencing and how they hope to approach these discussions in practice. While this was not the primary aim of the study, secondary gains of this nature could increase overall awareness of the complications introduced by exome sequencing the need to prioritize aspects of informed consent. These results suggest that genetic counselors strongly value collaborative decision-making and ensuring patient understanding. These priorities should inform future training initiatives that prepare healthcare providers across all disciplines to incorporate exome sequencing into their clinical and research practices.

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APPENDIX A: Recruitment Email

Dear NSGC Member,

My name is Rachel Gore and I am a third-year student in the Johns Hopkins/NHGRI Genetic Counseling Training Program. I would like to invite you to participate in a research study as part of my master's thesis exploring **challenges to obtaining informed consent for exome sequencing**. The aim of this study is to better understand how genetic counselors approach the informed consent process and how they perceive challenges in this area. These questions are relevant to all genetic counselors, as they address the fundamental goal of improving consent practice for patients, research participants, and laboratory clients considering the benefits and limitations of exome sequencing.

Study Information:

- **All practicing genetic counselors** in any clinical specialty, laboratory or research setting are welcome to participate - experience with exome sequencing is not required!
- The online survey will take **15-20 minutes.**
- You will **not** be asked to provide any personally identifying information.
- Participation in this study is entirely **voluntary**; you may stop at any time.
- To thank you for your time, all participants will receive a **$10 Amazon gift card**. You will have the option to enter contact information following completion of the survey. This information will not be linked to your responses, which are anonymous.

Please click here to access the survey: *https://www.surveymonkey.com/r/exomeconsent*

If you have any questions about this research project, please feel free to contact me at rachel.gore@nih.gov or my advisor, Barbara Biesecker, at barbarab@mail.nih.gov.

Thank you for your time and consideration.

Sincerely,
Rachel Gore, BA
ScM Candidate 2018
JHU/NHGRI GCTP

Barbara B. Biesecker, PhD
Director, JHU/NHGRI GCTP

APPENDIX B: Focus Group Consent Form

Challenges to the Informed Consent Process for Whole Exome Sequencing
Phase I: Focus Groups

What you should know about this study

- You are being asked to participate in a focus group for research purposes.
- Please read this consent form carefully and take as much time as you need.
- You are a volunteer. You can choose not to take part and you may leave the focus group at any time.

Purpose of research project

We would like to learn more about challenges to the informed consent process for whole exome sequencing as experienced by genetic counselors. Results gathered from this focus group will guide the design of an online survey that will be sent to a larger group of genetic counselors in the next phase of this study.

Why you are being asked to participate

You are being asked to join this study because you have professional experience with the informed consent process for whole exome sequencing in a clinical or research setting.

Procedures

During the focus group, you will be asked to discuss your experiences obtaining informed consent for whole exome sequencing, and aspects of this process that you have found challenging. You will also be asked to provide feedback about a list of potential challenges that we will provide. You will not be asked any questions about your personal life, or about specific cases or patients. Focus groups will be audio recorded, and the student investigator may also take written notes. The focus group is scheduled to take 30-45 minutes.

Risks/discomforts

There are no physical risks to being in this study. There is a risk that this study will cause a minor invasion of your privacy, as we will be discussing professional experiences. There is also a minor risk for discomfort if your answers disagree with the rest of the group, we expect that all participants will be respectful and honest in their responses.

Benefits

You may be interested in or learn from the experiences shared by other focus group participants. We hope that this focus group will help us to design a more effective survey so that we can gather meaningful information about perceived barriers to implementing whole exome sequencing in clinical and research settings.

Protecting data confidentiality

We will not collect any identifying information during the focus group, and the signed consent forms will be stored in a locked filing cabinet separately from the data.

Who can I contact if I have additional questions?
Call the student investigator, Rachel Gore, if you have questions. Any questions that cannot be answered by the student investigator will be forwarded to the senior investigator.

E-mail: rgore2@jhu.edu
Telephone: 617-833-3010

What does your signature on this consent form mean?

Your signature on this form means:

- You have been informed about this study's purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

_____	_____	_____
Print name	Signature	Date

_____	_____	_____
Print name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date

APPENDIX C: Survey Consent Form

Challenges to the Informed Consent Process for Whole Exome Sequencing
Phase II: Online Survey

Thank you for your interest in this survey!

We are conducting a research study about genetic counselor's preceptions about the challenges to obtaining informed consent for clinical whole exome sequencing. You are being asked to participate because you are a practicing genetic counselor and a member of the National Society of Genetic Counselors. You are eligible to participate whether or not you have had direct experience with whole exome sequencing.

Responding to this survey request is voluntary; it is your choice. Completing this survey and submitting it to us means you consent to participate in the study. You may choose not to answer any question that we ask.

This survey will take about 20 minutes, and will ask that you consider the challenges to obtaining informed consent for whole exome sequencing in a hypothetical scenario. We will not ask you for any personal or identifiable information, and you will not be prompted to share any information about your patients.

If you choose to complete the survey, you will have the option of providing contact information to receive a $10 gift card to tahnk you for your participation. This information will not be linked to your survey responses.

This project is being conducted by the National Human Genome Research Institute (NHGRI) as part of a masters thesis project. If you have any questions about the survey or study, please feel free to contact the student investigator, Rachel Gore (rachel.gore@nih.gov)

APPENDIX D: BWS Attribute List

1. Explaining the technological complexities of sequencing: Defining genetics/genomics concepts (e.g. genes, exons and mutations), and the process used to sequence all known coding regions of the genome in a single test.

2. Deliberating about secondary findings and their implications: describing the possibility that sequencing could identify a mutation in a gene that is unrelated to the primary indication for testing, but is associated with increased risk for a preventable or treatable disease.

3. Explaining the evolution of variant interpretation: classification of sequencing results may vary based on laboratory practices and may also change over time as more data is collected.

4. Assessing patient understanding of key content: using verbal and non-verbal cues to determine whether the patient has understood the risks, benefits and limitations of whole exome sequencing so that they can make an informed decision about testing.

5. Managing patient expectations about the results: communicating the inability to predict whether the test will yield results that impact diagnosis, treatment or daily life.

6. Explaining the meaning of a negative result: testing may not identify any variants, but this does not rule out the possibility that there is an underlying genetic cause that could not be detected by sequencing.

7. Conveying potential implications for relatives: if testing identifies a genetic cause for the patient's symptoms or a secondary finding, it is possible that other family members are at risk for the same condition and may need help communicating this information or pursuing follow-up testing.

8. Warning for insurance discrimination: though the Genetic Information Nondiscrimination Act (GINA) prevents health insurance companies from requesting or altering coverage based on genetic information, GINA does not protect against the risk of discrimination by companies selling life, disability or long-term insurance.

9. Tailoring consent based on indication and context: the parents in this scenario may have different consent needs due to their previous experience with genetic testing, than patients in a research setting or other specialty.

10. Engaging patients in collaborative decision-making: encouraging a dialogue in which patients discuss the risks and benefits they are considering when making a decision about whether or not to consent to undergoing sequencing.

11. Explaining variants of uncertain significance: it is possible that sequencing will identify a genetic change, but there will not be enough information available to determine whether or not this variant is the underlying cause of the patient's symptoms.

APPENDIX E: Survey

Challenges to the Informed Consent Process for Whole Exome Sequencing
Phase II: Online Survey

Student Investigator: Rachel Gore
NHGRI/JHU Genetic Counseling Training Program

Senior Investigator: Barbara Biesecker, PhD
NHGRI Social and Behavioral Research Branch

Please complete the following questions about yourself and your experience as a genetic counselor:

How old are you? (*fill in)*

What is your gender?

Male *Female* *Prefer to self-describe: (fill in)*

With which racial or ethnic group do you most identify?

Caucasian *African American* *Hispanic* *Asian* *Other*

For how many years have you been a practicing genetic counselor?

< 5 *5-9* *10-19* *20-29* *30 +*

What geographic region of the United States do you practice in?

Northeast *Midwest* *South* *West* *Other*

Which best reflects the greatest percentage of your current work responsibilities?

Clinical Care *Research* *Laboratory* *Other*

How would you best describe your current specialty?

Pediatrics *Prenatal* *Cancer* *Other*

How many times have you obtained informed consent for whole exome sequencing? (For either clinical or research purposes)

0 *1-9* *10-29* *30-49* *50+*

For the next section, mark your level of agreement with the following statements:

"It really disturbs me when I am not able to follow another person's train of thought"

1	*2*	*3*	*4*	*5*
Not at all characteristic of me				*Entirely characteristic of me*

"If I am uncertain about the responsibilities involved in a particular task, I get very anxious"

1	*2*	*3*	*4*	*5*
Not at all characteristic of me				*Entirely characteristic of me*

"Before any important task, I must know how long it will take"

1	*2*	*3*	*4*	*5*
Not at all characteristic of me				*Entirely characteristic of me*

"I don't like to work on a problem unless there is a possibility of getting a clear-cut and unambiguous answer"

1	*2*	*3*	*4*	*5*
Not at all characteristic of me				*Entirely characteristic of me*

"The best part of working on a jigsaw puzzle is putting in that last piece"

1	*2*	*3*	*4*	*5*
Not at all characteristic of me				*Entirely characteristic of me*

"I am often uncomfortable with people unless I feel that I can understand their behavior"

1	*2*	*3*	*4*	*5*
Not at all characteristic of me				*Entirely characteristic of me*

"A good task is one in which what is to be done and how it is to be done are always clear"

1	*2*	*3*	*4*	*5*
Not at all characteristic of me				*Entirely characteristic of me*

Please answer the following questions about whole exome sequencing using your current knowledge:

Whole exome sequencing can find variants in many genes at once.

True *False*

Whole exome sequencing will find variants that cannot be interpreted at the present time.

True *False*

Whole exome sequencing could find that a person has a high risk for a disorder even if they do not have symptoms.

True *False*

Whole exome sequencing may not find the cause of a disorder even if it is genetic.

True *False*

The gene variants that whole exome sequencing can find today could have different meanings in the future as scientists learn more about how genes work.

True *False*

Whole exome sequencing will not find any variants in people who are healthy.

True *False*

For the remainder of the survey questions, consider your response to the following scenario:

Samuel is a seven-year-old male with a history of global developmental delay that first presented at age eighteen months with delays in growth, walking, and speech. He passed his newborn hearing and vision screenings, and has had a normal brain MRI. He received early intervention services and is currently in school in a special education program. He has previously been evaluated in the general genetics clinic and has had karyotype and microarray analyses as well as Fragile X testing that were all normal. He was offered a follow-up appointment at the clinic for further diagnostic testing through whole exome sequencing that has recently become available. He will be accompanied by his parents. This is your first time meeting the family, and you have an hour scheduled to complete the informed consent process.

"I am confident in my ability to communicate the benefits and limitations of whole exome sequencing to this family"

1 2 3 4 5 6 7
Strongly Disagree *Strongly Agree*

"I know what to say to explain the types of potential results they could receive"

1 2 3 4 5 6 7
Strongly Disagree *Strongly Agree*

"Samuel's parents will be able to manage the scope of information in the informed consent process"

1 2 3 4 5 6 7
Strongly Disagree *Strongly Agree*

"Samuel's parents have the ability to make an informed decision about whole exome sequencing"

1 2 3 4 5 6 7
Strongly Disagree *Strongly Agree*

For the next sections of the survey you will be presented with a series of counseling elements that are part of the process of obtaining informed consent for whole exome sequencing. Please review all of the elements before beginning this section of the survey; you will be able to access the explanations of each item again at any point during the survey:

Rate the degree to which you feel that each of these is challenging to do well:
(Sliding scale from 0 to 100)

1. Describing the technological complexities of sequencing

2. Deliberating about the implications of secondary findings

3. Explaining the evolution of variant interpretation

4. Assessing patient understanding of key content

5. Managing patient expectations about the results

6. Clarifying the meaning of a negative result

7. Conveying potential implications for relatives

8. Warning for insurance discrimination

9. Tailoring consent based on indication and context

10. Engaging patients in collaborative decision-making

11. Explaining variants of uncertain significance

You will now be presented with a series of choice sets containing five of these counseling elements. For each set of counseling elements, please select the one that you think is **most important** and the one that is **least important** to obtaining meaningful informed consent from Samuel's parents. You will be asked this question repeatedly with different counseling elements. You may review explanations of each element at the bottom of the page.
(*Sample choice sets, eleven were presented in total)*

Most Important	Counseling Elements of Informed Consent for WES	Least Important
O	Describing the technological complexities of sequencing	O
O	Assessing patient understanding of key content	O
O	Conveying potential implications for relatives	O
O	Tailoring consent to the indication and context	O
O	Explaining variants of uncertain significance	O

Most Important	Counseling Elements of Informed Consent for WES	Least Important
O	Deliberating about the implications of secondary findings	O
O	Assessing patient understanding of key content	O
O	Managing patient expectations about results	O
O	Clarifying the meaning of a negative result	O
O	Explaining variants of uncertain significance	O

Please take some time to answer the following questions in your own words:

Are Samuel and his parents comparable to patients that you would expect to see in your practice?

Yes *No*

How so?

What concerns do you have about approaching the informed consent process for whole exome sequencing with Samuel and his parents?

What concerns do you expect Samuel's parents to have about whole exome sequencing?

Describe your experience completing the most-least challenging exercise. Did you feel it was challenging to select one option? If so, what was most difficult?

Please provide any additional comments about your experience taking this survey:

CURRICULUM VITAE

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National Human Genome Research Institute/Johns Hopkins University
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Date December 13, 2017

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Education

2009 - 2013 B.A., Biology, Clark University (Summa Cum Laude)
Thesis Advisor – Dr. Justin Thackeray, "Genetic Analysis of Growth Factor Signaling Inhibitors in *Drosophila"*

2015 - present ScM anticipated 2018, Genetic Counseling, Johns Hopkins Bloomberg School of Public Health
Thesis Advisor – Dr. Barbara B. Biesecker, "Challenges to Informed Consent for Exome Sequencing: A Best Worst Scaling Experiment"

Employment History

2008-2009 Optometry Technician, NewtonEye P.C.
2013-2015 Medical Assistant, Internal Medicine, Harvard Vanguard Medical Associates

Professional Society Membership

2016-present Guest Member, National Society of Genetic Counselors

Honors And Awards

2009 Traina Scholarship for the Sciences, Clark University, awarded for distinguished performance in biological sciences

2010 CRC Press Chemistry Achievement Award, Clark University, awarded for distinguished clinical performance as an intern

Clinical Activities

2015-present Graduate Student Clinical Rotations in Genetic Counseling (pediatric, adult, cancer, prenatal, and laboratory)

Institutional Service

2015-2017 Member at Large, Health Behavior and Society Student Organization

Teaching Service

Undergraduate Student Teaching

2013 Teaching Assistant, Medical Ethics Course
30 undergraduates, weekly discussion groups and monthly study review

2013 Peer Advisor, Clark University
7 first-year undergraduates, provided academic advising

Publications

Peer-reviewed journal articles

1. Denton, K, Atkinson, M, Borenstein, S, Carlson, A, Carroll, T, Cullity, K, DeMarsico C, Ellowitz, D, Gialtourides A, **Gore, R**, Herleikson, A, Ling, A, Martin, R, McMahan, K, Naksukpaiboon P, Seiz, A, Yearwood, K, O'Neill, J, Wiatrowski, H. Identification of a possible respiratory arsenate reductase in Denitrovibrio acetiphilus, a member of the phylum Defferibacteres. Archives of Microbiology. 2013 Jul;195:661-670. *(ran analyses)*

Submitted journal articles

1. **Gore, R.,** Biesecker BB. Challenges to informed consent for genomic sequencing: a systematic literature review. European Journal of Human Genetics. 2017 (Submitted).

Proffered Communications

1. **Gore, R**. Biesecker, BB, Cohen, J., Challenges to informed consent for exome sequencing: a best worst scaling experiment, NHGRI Research Symposium, Bethesda MD, Poster Presentation, 2017